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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,815	02/18/2005	Erich Gulbins	26610U	1995

20529 7590 03/30/2009

THE NATH LAW GROUP
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Alexandria, VA 22314

EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
03/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,815	GULBINS, ERICH	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continuation Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/07/09 has been entered.

Response to Arguments

This Office Action is in response to the amendment submitted on 01/07/2009. Claims 40-46 are pending in the applications, with claims 1-39 having being cancelled. Accordingly, claims 40-46 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Examiner further acknowledges amendment of the specification. Given that applicant has submitted both a substitute specification showing all the changes with the appropriate markings and provided an accompanying clean version, and no new matter was introduced, the Examiner maintains that such specification does indeed conformed to 37 CFR 1.125(b) and (c). Thus, the revised specification is acknowledged and has been entered.

Applicant's arguments against the 35 U.S.C. 112, first paragraph and § 103(a) rejection of claims 37-39 over Grassme in view of Albouz have been fully considered. Applicant argues that the submission of the new claims overcome these rejections. While the Examiner disagrees with applicant's assertion, the rejections are nonetheless moot since claims 37-39 are now cancelled. Consequently, the rejections of claims 37-39 under 35 U.S.C. 112, first paragraph and § 103(a) are hereby withdrawn.

For the foregoing reasons, the rejections of record are withdrawn. However, in view of applicant's cancellation and addition of claims 40-46, the following modified 103 (a) Non- Final rejections are being made.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As stated by the court in Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886, 1892 (CAFC 2004), regarding the written description requirement:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice.... The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described.

In this instant application, applicant did not specifically describe what compounds are encompassed by the term "substance derived from a tricyclic antidepressant" or what compound is encompassed by the term "substance-derived from a tetracyclic antidepressant" in the claim(s) (i.e. claim 40) or in the specification (see specification pg. 9, lines 5-20, and pg. 11, lines 30-39). Thus, the Examiner contends that due to the failure of applicant to sufficiently describe the particular tetracyclic or tricyclic derived-substances, it would be impossible for one skilled in the art to envisage what is truly meant by substance-derived from tricyclic or tetracyclic antidepressant. Consequently, due to this lack of written description, the exact interpretation of substance-derived from tricyclic or tetracyclic antidepressants being claimed by applicant cannot be fully ascertained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40, 42, and 44 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Grassme et al. (Nature Medicine, March 2003, Vol. 9, No. 3, pgs. 322-330, previously submitted) in view of Albouz et al. (Neuro. Sci. Letters, 1983, Vo. 36, pg. 311-315, previously cited).

Grassme et al. teach that P. aeruginosa is one of the most severe infections that affects patients with cystic fibrosis (see Introduction, pg. 322, left col., paragraph 1). In fact, recurrent infection of P. aeruginosa often leads to pneumonia, a primary cause of lung destruction in patients with cystic fibrosis (see Introduction, pg. 322, left col., paragraph 1). Grassme also teaches that sphingolipid-enriched platforms (i.e. rafts), signaling-induced platforms, are induced by the bacterium P. aeruginosa (see pg. 322, Introduction, left col.). It does so by inducing clustering of the cystic fibrosis transmembrane conductance regulator molecule (i.e. CFTR) implicated in P. aeruginosa internalization and via the induction of apoptosis in the bronchi as detected through *in vivo* analysis (see pg. 323 and pg. 324, left col.). Moreover, Grassme determined that modulation of the signaling platforms led to the release of pro-inflammatory cytokines after infection with P. aeruginosa (see pg. 324, right col.). Additionally, the study of Grassme demonstrated that infection by P. aeruginosa activates Acid sphingomyelinase (i.e. ASM), translocates it to the extracellular leaflets of cells in the bacteria containing-raft platforms and release ceramide in an non-tissue specific manner (i.e. the same observation in all tissues suggesting the same mechanism is operating in the lungs of cystic fibrosis patients; see pg. 325-236). Grassme et al. further suggest that infection

with P. aeruginosa triggers ASM surface translocation where its activation causes release of deleterious cytokines such as IL-1 and imbalance of ceramide, an apoptosis inducing molecule (see pg. 327, left col.) along with internalization of the bacterium into the host cell which consequently leads to pneumonia and eventual death in mice models(see pg. 327). In summary, Grassme et al. teach that modification of sphingolipid-rich rafts and generation of larger platforms due to activation of ASM-induced release of ceramide play a role in the defense against P. aeruginosa infection (see pg. 328, right col.). The study of Grassme et al. therefore suggests that targeting molecules that modulates signaling platforms (such as ASM) should provide novel therapeutic treatment against P. aeruginosa, an infection found in cystic fibrosis.

Grassme et al. do not teach therapeutic compounds for the treatment of cystic fibrosis.

Albouz et al., on the other hand, teach the use of tricyclic antidepressants in decreasing ASM activity (see abstract). Importantly, Albouz et al. teaches that both the tricyclic antidepressants imipramine and desimipramine (instant claims 40, 42, and 44) are effective in drastically reducing ASM in cultured fibroblasts (see pg. 312, paragraph 1). Albouz et al. further tested other cells (i.e. other cells in other tissues) including glioma cells (i.e. brain cells) in the presence of both imipramine and desimipramine and found a reduction in sphingomyelinase activity in a dose-dependent, time-dependent, non-tissue specific manner(pgs. 312, last paragraph, 314, top paragraph; and see tables 1-2). Importantly, Albouz et al. suggest that the concentration used for the

observed reduction mimics dosage that can modify membrane fluidity physiologically; thereby suggesting *in vivo* application (see pg. 314, last paragraph).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the tricyclic depressants of Albouz et al. such as imipramine to inactivate ASM since Grassme et al. teach that ASM activation leads to modulation of signaling and internalization of P.aeruginosa, the bacterium involved in cystic fibrosis and given that Albouz et al. teach that tricyclic depressants can reduce ASM and therefore all the side effects associated with activation of ASM. Given the teachings of Grassme and Albouz, one of ordinary skill in the art would have been motivated to utilize imipramine in the treatment of cystic fibrosis with the reasonable expectation of providing a method efficient in treating cystic fibrosis and pneumonia-induced by P. aeruginosa.

Claim 43 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Grassme et al. (Nature Medicine, March 2003, Vol. 9, No. 3, pgs. 322-330, previously submitted) in view of Albouz et al. (Neuro. Sci. Letters, 1983, Vo. 36, pg. 311-315, previously cited) as applied to claims 40, 42, and 44 and in further view of Bilgi et al. (Canadian Family Physician. May 1979; Vol. 25, pgs. 619-620, 622, and 624-625).

The Grassme and Albouz references are as discussed above and incorporated by reference herein. However, Grassme and Albouz do not teach the antidepressant as a tetracyclic antidepressant or that amitryptiline as the tricyclic antidepressant.

Bilgi et al. teach that tricyclic antidepressants (TCA) are effective in treating depressive states but may impose minor therapeutic side effects (se pg. 619, left col.). Indeed, Bilgi et al. teach that treatment with tricyclic antidepressants such as amitriptyline, imipramine, and clomipramine caused various side effects including hypotension, hypertension, arrhythmia, and sinus tachycardia (see pg. 620 and pg. 624, table 1). As for the tetracyclic antidepressant, maprotiline, Bilgi et al. teach that administration of maprotiline to healthy individuals resulted in minimal ST-T changes which later disappeared despite repeated administration of the compound (see pg. 622, right col., Paragraph 1 under maprotiline and its effects Section). In fact, Bilgi et al. teach that treatment with maprotiline can be given safely to cardiac patients as it improves ventricular function, end-diastolic pressure, and stroke work index and further suggest treatments with tetracyclic antidepressants to patients predisposed to cardiotoxicity to TCA (see pg. 622, right col., and pg. 625, Conclusion Section).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the TCA amitryptiline of Bilgi et al. instead of the TCA of Albouz et al. since Bilgi et al. teach them as equivalent TCA. Furthermore, it is considered that one of ordinary skill in the art at the time of the invention was made

would have found it obvious to substitute amitryptiline for imipramine given that the substitution of one known element for another would have yielded predictable results. Moreover, one of ordinary skill in the art would have found it obvious to utilize tetracyclic antidepressants as opposed to TCA since Bilgi et al. teach that tetracyclics pose minimal side effects and lead to improved ventricular function. Thus, given the teachings of Bilgi et al., one of ordinary skill in the art would have been motivated to substitute amitryptiline or tetracyclics for the imipramine of Albouz in the treatment of cystic fibrosis with the reasonable expectation of providing a method efficient in treating cystic fibrosis and a method with minimal side effects.

Claims 41 and 45-46 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Grassme et al. (Nature Medicine, March 2003, Vol. 9, No. 3, pgs. 322-330, previously submitted) in view of Albouz et al. (Neuro. Sci. Letters, 1983, Vo. 36, pg. 311-315, previously cited) as applied to claims 40, 42, and 44 and in further view of Bilgi et al. (Canadian Family Physician. May 1979; Vol. 25, pgs. 619-620, 622, and 624-625) as applied to claim 43 and in further view of Daines (U.S. 5,569,677).

The Grassme, Albouz, and Bilgi references are as discussed above and incorporated by reference herein. However, Grassme, Albouz, and Bilgi do not teach the formulation as an inhalation formulation.

Daines teaches pharmaceutical compositions containing leukotriene antagonists known to be useful in various diseases including cystic fibrosis (see abstract and col. 1, lines 40-45). Daines teaches that such compositions can contain a pharmaceutically carrier or diluent depending upon the intended route of administration, for example parenterally, topically, orally, or by inhalation (see col.7, lines 34-37, 52-55, and col. 11, example 3).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to formulate the composition as an inhalation composition since Daines teaches that compositions for the treatment of cystic fibrosis can be formulated in various forms including inhalation. Moreover, it is well within the purview of the skilled artisan during routine experimentation to formulate the composition in various forms depending on desired ease of administration or desired rate of delivery of such composition. Thus, given the teachings of Daines, one of ordinary skill in the art would have been motivated to formulate the modified composition of Grassme and Albouz as an inhalation composition for the treatment of cystic fibrosis with the reasonable expectation of providing a method efficient in treating cystic fibrosis and a method efficient in delivering TCA or tetracyclics.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

03/24/2009

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617